Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	302	(cerebral adj vascular adj disease)	USPAT	OR	OFF	2005/06/30 14:41
L2	717	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury)) near6 (blood adj flow)	USPAT	OR	OFF	2005/06/30 14:42
L3	25624	l1 or "l3"	USPAT	OR	OFF	2005/06/30 14:42
L4	1009	l1 or l2	USPAT	OR	OFF	2005/06/30 14:43
L5	0	l4 near10 HET0016	USPAT	OR	OFF	2005/06/30 14:43
L6	252	(HETE or (cytochrome adj P450 adj fatty adj acid adj omega adj hydroxylase)) near6 (inhibit or inhibitor or inhibition or inhibiting)	USPAT	OR	OFF	2005/06/30 14:56
L7	8	l6 and l4	USPAT	OR	OFF	2005/06/30 14:46

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	302	(cerebral adj vascular adj disease)	USPAT	OR	OFF	2005/06/30 14:41
L2	717	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury)) near6 (blood adj flow)	USPAT	OR	OFF	2005/06/30 15:09
L3	25624	l1 or "l3"	USPAT	OR	OFF	2005/06/30 14:42
L4	1009	l1 or l2	USPAT	OR	OFF	2005/06/30 14:43
L5	0	l4 near10 HET0016	USPAT	OR	OFF	2005/06/30 14:43
L6	252	(HETE or (cytochrome adj P450 adj fatty adj acid adj omega adj hydroxylase)) near6 (inhibit or inhibitor or inhibition or inhibiting)	USPAT	OR	OFF	2005/06/30 14:56
L7	8	l6 and l4	USPAT	OR	OFF	2005/06/30 14:46
L8	160149	(stroke or migraine or vasospasm or (head adj injury) or (brain adj injury))	USPAT	OR	OFF	2005/06/30 15:09
L9	160268	L1 or L8	USPAT	OR	OFF	2005/06/30 15:09
L10	0	L9 near10 HET0016	USPAT	OR	OFF	2005/06/30 15:10
L11	52	L6 and L8	USPAT	OR	OFF	2005/06/30 15:11
L12	0	L11 and HET0016	USPAT	OR	OFF	2005/06/30 15:11

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NEWS 12 APR 04 EPFULL enhanced with additional patent information and new
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may be affected by a change in filing date for U.S. applications.
NEWS 16 APR 28 Improved searching of U.S. Patent Classifications for
U.S. patent records in CA/CAplus
NEWS 17 MAY 23 GBFULL enhanced with patent drawing images
NEWS 18 MAY 23 REGISTRY has been enhanced with source information from
CHEMCATS
NEWS 19 JUN 06 STN Patent Forums to be held in June 2005

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                  (Version 8.0 for Windows) now available
 NEWS  21 JUN 13  RUSSIAPAT: New full-text patent database on STN
 NEWS  22 JUN 13  FRFULL enhanced with patent drawing images
 NEWS  23 JUN 20  MEDICONF to be removed from STN
 NEWS  24 JUN 27  MARPAT displays enhanced with expanded G-group
definitions
                  and text labels

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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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=> s (cerebral vascular disease) or stroke or migraine or vasospasm
or (head injury) or (brain injury) or Alzheimer's or dementia or
Parkinson's or Huntington
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L1      476195 (CEREBRAL VASCULAR DISEASE) OR STROKE OR MIGRAINE OR
VASOSPASM
               OR (HEAD INJURY) OR (BRAIN INJURY) OR ALZHEIMER'S OR
DEMENTIA
               OR PARKINSON'S OR HUNTINGTON

=> s l1 (10A) HET0016
L2            1 L1 (10A) HET0016

=> d l2 bib ab

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:353270  CAPLUS
DN   136:363861
TI   Use of 20-HETE synthesizing enzyme inhibitors as therapy for
cerebral
     vascular diseases
IN   Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato,
Masakazu;
     Kameo, Kazuya; Okuyama, Shigeru
PA   MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co.,
Ltd.
SO   PCT Int. Appl., 38 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.
DATE
     ---------------     ----   --------    --------------------
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PI   WO 2002036108        A2    20020510    WO 2001-US27605
20010906
     WO 2002036108        A3    20021017
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CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,
PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
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        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE,
CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG
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CA 2427557 AA 20020510 CA 2001-2427557
20010906
AU 2001088798 A5 20020515 AU 2001-88798
20010906
EP 1330240 A2 20030730 EP 2001-968558
20010906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE,
MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004512361 T2 20040422 JP 2002-538920
20010906
PRAI US 2000-245638P P 20001103
WO 2001-US27605 W 20010906
AB A method for treating cerebral vascular diseases in a human or
non-human
animal is disclosed. The method involves inhibiting 20-HETE
synthesizing
enzyme activity sufficiently to increase or prevent a decrease
in cerebral
blood flow in the human or non-human animal.

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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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=> s (cerebral vascular disease) or stroke or migraine or vasospasm
or (head injury) or (brain injury) or Alzheimer's or dementia or
Parkinson's or Huntington
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L1      476195 (CEREBRAL VASCULAR DISEASE) OR STROKE OR MIGRAINE OR
VASOSPASM
               OR (HEAD INJURY) OR (BRAIN INJURY) OR ALZHEIMER'S OR
DEMENTIA
               OR PARKINSON'S OR HUNTINGTON

=> s l1 (10A) HET0016
L2            1 L1 (10A) HET0016

=> d l2 bib ab

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:353270  CAPLUS
DN   136:363861
TI   Use of 20-HETE synthesizing enzyme inhibitors as therapy for
cerebral
     vascular diseases
IN   Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato,
Masakazu;
     Kameo, Kazuya; Okuyama, Shigeru
PA   MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co.,
Ltd.
SO   PCT Int. Appl., 38 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.
DATE
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PI   WO 2002036108        A2    20020510    WO 2001-US27605
20010906
     WO 2002036108        A3    20021017
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GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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PH, PL,
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CH, CY,
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TR, BF,
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     CA 2427557           AA    20020510    CA 2001-2427557
20010906
     AU 2001088798        A5    20020515    AU 2001-88798
20010906
     EP 1330240           A2    20030730    EP 2001-968558
20010906
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE,
MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     JP 2004512361        T2    20040422    JP 2002-538920
20010906
PRAI US 2000-245638P      P     20001103
     WO 2001-US27605      W     20010906
AB   A method for treating cerebral vascular diseases in a human or
non-human
     animal is disclosed.  The method involves inhibiting 20-HETE
synthesizing
     enzyme activity sufficiently to increase or prevent a decrease
in cerebral
     blood flow in the human or non-human animal.


=> s (20-HETE or (cytochrome P450 fatty acid omega hydroxylase)) (6A)
(inhibit or inhibitor or inhibition or inhibiting)
L3          351 (20-HETE OR (CYTOCHROME P450 FATTY ACID OMEGA
HYDROXYLASE))
                (6A) (INHIBIT OR INHIBITOR OR INHIBITION OR
INHIBITING)

=> s l1 and l3
L4            9 L1 AND L3

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DUPLICATE PREFERENCE IS 'MEDLINE, BIOSIS, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L4
L5            8 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)

=> s l1 and HET0016
L6            4 L1 AND HET0016

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ENTER L# LIST OR (END):l6
DUPLICATE PREFERENCE IS 'MEDLINE, BIOSIS, CAPLUS'
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PROCESSING COMPLETED FOR L6
L7            4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)

=> s l6 or l5
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L8 8 L6 OR L5

=> d l8 1-8 bib ab

L8 ANSWER 1 OF 8 MEDLINE on STN
AN 2004532827 MEDLINE
DN PubMed ID: 15503650
TI Mechanisms regulating cerebral blood flow as therapeutic targets.
AU Pratt Phillip F; Medhora Meetha; Harder David R
CS Cardiovascular Center, Department of Pharmacology and Toxicology, Medical
College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226,
USA.. ppratt@mcw.edu
NC HL-069996 (NHLBI)
HL-33833 (NHLBI)
HL-59996 (NHLBI)
HL-68769 (NHLBI)
SO Current opinion in investigational drugs (London, England : 2000), (2004
Sep) 5 (9) 952-6. Ref: 34
Journal code: 100965718. ISSN: 1472-4472.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 20041027
Last Updated on STN: 20050126
Entered Medline: 20050125
AB Regulation of cerebral blood flow (CBF) is critical for the maintenance of
neural function and hence survival of the organism. Since the brain does
not store glycogen, unlike muscle, a constant supply of glucose and oxygen
are needed for the minute-by-minute demands of cerebral function. This
review focuses on important lipid mediators that act as reciprocal
regulators of cerebral artery diameter and their potential as targets for
therapeutic intervention in diseases such as ischemia, **stroke**
and subarachnoid hemorrhage. Cytochrome P450 metabolism of arachidonic
acid to 20-hydroxyeicosatetraenoic acid (20-HETE) or epoxyeicosatrienoic
acids (EETs) provides a mechanism for the constriction and relaxation of

cerebral arteries, respectively. Additionally, EETs have mitogenic potential and may contribute to angiogenesis in the brain, which has important implications during recovery from cerebral injury. Finally, we discuss novel **inhibitors** of **20-HETE** formation and actions as well as interventions to enhance EET production in cerebrovascular disease.

L8 ANSWER 2 OF 8 MEDLINE on STN
AN 2003209741 MEDLINE
DN PubMed ID: 12677022
TI Contribution of 5-hydroxytryptamine1B receptors and 20-hydroxyeiscosatetraenoic acid to fall in cerebral blood flow after subarachnoid hemorrhage.
AU Cambj-Sapunar Liana; Yu Ming; Harder David R; Roman Richard J
CS Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226, USA.
SO Stroke; a journal of cerebral circulation, (2003 May) 34 (5) 1269-75.
Electronic Publication: 2003-04-03.
Journal code: 0235266. ISSN: 1524-4628.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030506
Last Updated on STN: 20030701
Entered Medline: 20030630
AB BACKGROUND AND PURPOSE: This study examined the interaction between 5-hydroxytryptamine1B (5-HT1B) receptors and 20-hydroxyeiscosatetraenoic acid (20-HETE) in contributing to the acute fall in regional cerebral blood flow (rCBF) after subarachnoid hemorrhage (SAH) in rats. METHODS: The effects of intracisternal injection of 0.3 mL of arterial blood, artificial cerebrospinal fluid, and 5-HT on rCBF and the levels of 20-HETE and 5-HT in cerebrospinal fluid were measured in rats pretreated with vehicle, a 5-HT1B receptor antagonist (isamoltane hemifumarate), or an **inhibitor** of the synthesis of **20-HETE** (**HET0016**). The effects of **HET0016** and isamoltane on the

vasoconstrictor response and changes in [Ca2+]i to 5-HT were also studied in middle cerebral arteries and vascular smooth muscle cells isolated from these vessels. RESULTS: 20-HETE and 5-HT levels in cerebrospinal fluid rose from 172+/-10 to 629+/-44 ng/mL and from 6+/-4 to 1163+/-200 nmol/mL, respectively, after SAH. rCBF fell by 30% 10 minutes after SAH, and it remained at this level for the next 2 hours. Blockade of 5-HT1B receptors prevented the sustained fall in rCBF seen after SAH. Intracisternal injection of 5-HT mimicked SAH by increasing 20-HETE levels in cerebrospinal fluid to 475+/-94 ng/mL and reducing rCBF by 30%. Blockade of the synthesis of 20-HETE with **HET0016** prevented the fall in rCBF produced by 5-HT. Isamoltane and **HET0016** reduced the vasoconstrictor response of isolated MCA to 5-HT by >60% and diminished the rise in [Ca2+]i produced by 5-HT in vascular smooth muscle cells isolated from these arteries. CONCLUSIONS: These results suggest that the release of 5-HT after SAH activates 5-HT1B receptors and the synthesis of 20-HETE and that 20-HETE contributes to the acute fall in rCBF by potentiating the vasoconstrictor response of cerebral vessels to 5-HT.

L8 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2004:204096 BIOSIS
DN PREV200400204639
TI Reduction of brain damage following focal cerebral ischemia by TS - 011, a 20 - hydroxyeicosatetraenoic acid synthesizing enzyme inhibitor.
AU Omura, T. [Reprint Author]; Miyata, N. [Reprint Author]; Tanaka, Y. [Reprint Author]; Kitano, K. [Reprint Author]; Koizumi, C. [Reprint Author]; Fukawasa, M. [Reprint Author]; Endo, H. [Reprint Author]; Hachiuma, K. [Reprint Author]; Minagawa, T. [Reprint Author]; Sakurai, T. [Reprint Author]; Yoshida, S. [Reprint Author]; Okuyama, S. [Reprint Author]; Nakaike, S. [Reprint Author]; Roman, R. J.; Harder, D. R.
CS Dept of Physiology, Taisho Pharmaceut. Co., Ltd, Saitama, Japan
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003)

Vol. 2003, pp. Abstract No. 741.5. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New
Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB 20-Hydroxyeicosatetraenoic acid (20-HETE) is one of the metabolites of
arachidonic acid catalyzed by CYP4A isozymes. **20-HETE** **inhibits** the large-conductance, Ca2+-activated K+-channel and increases Ca2+ influx through the voltage-gated Ca2+ channel. 20-HETE
potently constricts cerebral arteries from a variety of species through
these mechanisms. Recent studies have indicated that 20-HETE contributes
the acute fall in cerebral blood flow in rats following subarachnoid
hemorrhage. **Inhibition** of **20-HETE** formation
might increase collateral blood flow and be useful in reducing brain
damage following ischemic **stroke** as well. Recently, we developed the potent and selective **inhibitor** of **20-HETE** synthesizing enzyme, TS-011. The present study examined the
effects of TS-011 on infarct size following 1 hr of transient occlusion
and 23 hr of reperfusion of the middle cerebral artery occlusion (MCAO) of
rats. Plasma levels of 20-HETE increased significantly from 518 to 772
pg/mL 3 and 6 hours after occlusion and reperfuion of MCA. There was also
upregulation of the expression of CYP4A protein in the penumbra region of
infarct area in comparison to the contralateral hemisphere. Intravenous
infusion of TS-011 (0.1 mg/kg/hr) significantly reduced the infarct volume
by 35%. The reduction of infarct volume by TS-011 was even observed when
the compound was administered 4 hours after occlusion of the MCA. TS-011
prevented the increase in plasma 20-HETE levels following occlusion and
reperfusion of the MCA. TS-011 also reduced the infarct volume by 30 % in
a photochemically-induced model of permanent MCAO of rats. These results

suggest that **inhibition** of the production of **20-HETE** with TS-011 provides neuroprotection following ischemic **stroke**.

L8 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:89980 BIOSIS
DN PREV200300089980
TI An **Inhibitor** of **20-HETE** Formation Attenuates the Fall in Cerebral Blood Flow Following Subarachnoid Hemorrhage.
AU Okamoto, Hirotsugu [Reprint Author]; Maier, Kristopher G. [Reprint Author]; Harder, David R. [Reprint Author]; Roman, Richard J. [Reprint Author]
CS Physiology, Medical College of Wisconsin, Milwaukee, WI, USA
SO Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2002) No. 2000, pp. Abstract No. 736. http://www.asa-abstracts.com. cd-rom.
Meeting Info.: 2000 Annual Meeting of the American Society of Anesthesiologists. San Francisco, CA, USA. October 16-18, 2000. American Society of Anesthesiologists Inc.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 12 Feb 2003
Last Updated on STN: 12 Feb 2003
AB INTRODUCTION: Acute cerebral **vasospasm** following subarachnoid hemorrhage (SAH) causes ischemic **stroke**. Although endothelin, nitric oxide and thromboxane have been implicated to play a role in cerebral **vasospasm**, the relative importance of these mediators versus others have not been fully resolved. Recently, a cytochrome P450 metabolite of arachidonic acid, 20-hydroxyeicosatetraenoic acid (20-HETE)(a potent vasoconstrictor), has been reported to play a pivotal role in the regulation of cerebrovascular tone. To examine the role of 20-HETE in mediating acute cerebral **vasospasm**, we compared cerebral blood flow responses following SAH in rats treated with vehicle or an **inhibitor** of **20-HETE** formation,17-ODYA. METHODS: Experiments were performed on ketamine and thiobutabarbiturate anesthetized male Sprague-Dawley rats weighing 250-300 g. The animals were artificially ventilated and arterial pressure and

PCO2 levels were monitored. Regional cerebral blood flow (rCBF) was continuously measured with laser-Doppler flowmetry through thin closed cranial window over the parietal region of the cerebral cortex. SAH was induced by injecting 0.3 ml of arterial blood into the Cisterna Magna. 20-HETE levels were measured by fluorescent HPLC from samples drawn via Cisterna Magna before and after SAH. Rats were divided into two groups. In group 1 (n=7), rats were given an injection of 2 nmoles of 17-ODYA into the Cisterna Magna 1 hour prior to SAH. In group 2 (n=5), rats received vehicle. Data was expressed mean +-SEM and significance of differences was determined using ANOVA followed by a Duncan's test. RESULTS: In vehicle-treated rats, rCBF fell by 40% within 10 minutes after SAH, and it remained at this level for the 2 hour duration of the experiment. In contrast, the initial decrease in rCBF was significantly less in the rats pretreated with 17-ODYA, and rCBF returned to pre-SAH levels within 2 hours (See Figure). In vehicle-treated rats, 20-HETE levels in cerebrospinal fluid (CSF) increased significantly from 7.5+-4 ng/ml to 204+-13 ng/ml after injection of blood; while 20-HETE levels did not increase in the 17-ODYA treated rats. CONCLUSIONS: These results indicate that SAH markedly increased 20-HETE levels in CSF, and 17-ODYA prevented both the increase of 20-HETE levels and the fall in rCBF following SAH. 20-HETE, a cytochrome P450 metabolite of arachidonic acid, may contribute to acute cerebral **vasospasm** following SAH. Preventing the production of, or the actions of 20-HETE, after SAH may provide a new therapeutic approach for the treatment of SAH and cerebral **vasospasm**.

L8 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2002:271687 BIOSIS
DN PREV200200271687
TI 20-HETE contributes to the acute fall in cerebral blood flow after

subarachnoid hemorrhage in the rat.
AU Kehl, Franz; Cambj-Sapunar, Liana; Maier, Kristopher G.; Miyata, Noriyuki;
Kametani, Shunishi; Okamoto, Hirotsugu; Hudetz, Anthony G.; Schulte, Marie
L.; Zagorac, Drazen; Harder, David R.; Roman, Richard J. [Reprint author]
CS Dept. of Physiology, Medical College of Wisconsin, 8701 Watertown Plank
Rd., Milwaukee, WI, 53226, USA
rroman@mcw.edu
SO American Journal of Physiology, (April, 2002) Vol. 282, No. 4 Part 2, pp.
H1556-H1565. print.
CODEN: AJPHAP. ISSN: 0002-9513.
DT Article
LA English
ED Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002
AB This study examined the effects of blocking the formation of
20-hydroxyeicosatetraenoic acid (20-HETE) on the acute fall in cerebral
blood flow after subarachnoid hemorrhage (SAH) in the rat. In
vehicle-treated rats, regional cerebral blood flow (rCBF) measured with
laser-Doppler flowmetry fell by 30% 10 min after the injection of 0.3 ml
of arterial blood into the cisterna magna, and it remained at this level
for 2 h. Pretreatment with **inhibitors** of the formation of
20-HETE, 17-octadecynoic acid (17-ODYA; 1.5 nmol
intrathecally) and N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine (
HET0016; 10 mg/kg iv), reduced the initial fall in rCBF by 40%,
and rCBF fully recovered 1 h after induction of SAH. The concentration of
20-HETE in the cerebrospinal fluid rose from 12+-2 to 199+-17 ng/ml after
SAH in vehicle-treated rats. 20-HETE levels averaged only 15+-11 and
39+-13 ng/ml in rats pretreated with 17-ODYA or **HET0016**,
respectively. **HET0016** selectively inhibited the formation of
20-HETE in rat renal microsomes with an IC50 of <15 nM and human
recombinant CYP4A11, CYP4F2, and CYP4F3 enzymes with an IC50 of 42, 125,
and 100 nM, respectively. These results indicate that 20-HETE contributes
to the acute fall in rCBF after SAH in rats.

L8 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2001:252340 BIOSIS

DN PREV200100252340
TI Blockade of 20-HETE formation attenuates cerebral **vasospasm** after subarachnoid hemorrhage in the rat.
AU Kehl, Franz [Reprint author]; Okamoto, Hirotsugu [Reprint author]; Maier, Kristopher G. [Reprint author]; Miyata, Noriyuki; Kametani, Shunishi; Harder, David R. [Reprint author]; Roman, Richard J. [Reprint author]
CS Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A127. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002
AB Previous studies have reported that the formation of vasoconstrictor metabolites of arachidonic acid (AA) following subarachnoid hemorrhage (SAH) is elevated. Since the primary metabolite of AA in the cerebral circulation is 20-hydroxyeicosatetraenoic acid (20-HETE), the present study examined its role in the development of cerebral **vasospasm** following SAH in the rat. Regional cerebral blood flow (rCBF) was measured using laser Doppler flowmetry. SAH was induced by injection of 0.3 ml autologous arterial blood into the Cisterna Magna of rats that were pretreated with vehicle, a **20-HETE** and EET **inhibitor** 17-octadecynoic acid (17-ODYA) (1.5 nM, intrathecally), or a selective **inhibitor** of **20-HETE** formation, N-hydroxy-N'-(4-butyl-2-methylphenyl)-formamidine (**HET0016**) (10 mg/kg, i.v.). Cerebrospinal fluid (CSF) was collected before and after SAH and the effects of **HET0016** on the formation of 20-HETE in rat renal cortical microsomes were determined. In control rats, rCBF fell 30% 10 min after the induction of SAH and remained at this level for the 2 hr duration of the experiment. Pretreatment of the rats with 17-ODYA or **HET0016** reduced the initial fall in

rCBF at 10 min by 40% and rCBF fully recovered to control values 90 min after induction of SAH. The 20-HETE concentration in CSF averaged 180+-10 ng/ml after SAH in control animals and only 15+-5 and 60+-10 ng/ml in rats treated with 17-ODYA or **HET0016**. **HET0016** selectively inhibited the formation of 20-HETE by renal microsomes with an IC50 of 15 nM. It had no effect on epoxygenase activity even at a concentration of 1000 nM. The results of the present study indicate that the levels of 20-HETE are elevated in CSF following SAH and that CYP4A inhibitors are effective in preventing the **vasospasm** in rats in vivo and have potential as therapeutic agents.

L8 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:147800 CAPLUS
DN 140:399863
TI Effects of a 20-HETE antagonist and agonists on cerebral vascular tone
AU Yu, Ming; Cambj-Sapunar, Liana; Kehl, Franz; Maier, Kristopher G.; Takeuchi, Kazuhiko; Miyata, Noriyuki; Ishimoto, Tsuyoshi; Reddy, L. Manmohan; Falck, John R.; Gebremedhin, Debebe; Harder, David R.; Roman, Richard J.
CS Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SO European Journal of Pharmacology (2004), 486(3), 297-306
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB This study examined the effects of a 20-hydroxyeicosatetraenoic acid (20-HETE) antagonist, 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid (WIT002) and two agonists, 4-amino-N-(20-hydroxy-eicosa-5(Z),14(Z)-dienoyl) benzenesulfonamide (ABSA) and 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (WIT003), on the diameter of rat middle cerebral arteries in vitro and on cerebral blood flow in vivo. WIT003, ABSA and 20-HETE all had a similar effect to reduce the diameter of the middle cerebral artery by 26%. WIT003

and 20-HETE both increased intracellular Ca2+ concentration ([Ca2+]i) in vascular smooth muscle cells isolated from the middle cerebral artery. In contrast, WIT002 had no effect on the basal diameter of the middle cerebral artery but it attenuated the vasoconstrictor responses and the rise in [Ca2+]i in vascular smooth muscle cells following administration of 20-HETE and 5-hydroxytryptamine (5-HT). WIT003 partially restored the vasoconstrictor response to 5-HT in the middle cerebral artery after administration of an **inhibitor** of the endogenous synthesis of **20-HETE**. Infusion of the 20-HETE agonists, WIT003 and ABSA, into cisterna magna of rats reduced baseline cerebral blood flow by 20%, whereas administration of the 20-HETE antagonist, WIT002, had no effect. Intracisternal injection of WIT002 attenuated the fall in cerebral blood flow following injection of blood into the cisterna magna, whereas administration of the 20-HETE agonist, ABSA, potentiated this response. These findings indicate that the 20-HETE agonists, WIT003 and ABSA, increase cerebral vascular tone both in vivo and in vitro and suggest blocking the vasoconstrictor actions of 20-HETE may be useful to prevent the acute fall in cerebral blood flow following subarachnoid hemorrhage.

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:353270 CAPLUS
DN 136:363861
TI Use of **20-HETE** synthesizing enzyme **inhibitors** as therapy for **cerebral vascular diseases**
IN Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato, Masakazu; Kameo, Kazuya; Okuyama, Shigeru
PA MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co., Ltd.
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002036108	A2	20020510	WO 2001-US27605	20010906
	WO 2002036108	A3	20021017		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2427557	AA	20020510	CA 2001-2427557	20010906
	AU 2001088798	A5	20020515	AU 2001-88798	20010906
	EP 1330240	A2	20030730	EP 2001-968558	20010906
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004512361	T2	20040422	JP 2002-538920	20010906
PRAI	US 2000-245638P	P	20001103		
	WO 2001-US27605	W	20010906		

AB A method for treating **cerebral vascular diseases** in a human or non-human animal is disclosed. The method involves **inhibiting 20-HETE** synthesizing enzyme activity sufficiently to increase or prevent a decrease in cerebral blood flow in the human or non-human animal.